Recurrent cyanotic episodes with severe arterial hypoxaemia and intrapulmonary shunting: a mechanism for sudden death

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Abstract

The pathophysiology of recurrent cyanotic episodes has been investigated in 51 infants and children. Episodes began at a median age of 7 weeks (range 1 day to 22 months, 39 at less than 4 months). They were characterised by the rapidity of onset and progression of severe hypoxaemia with early loss of consciousness from cerebral hypoxia. The most common precipitating factor was a sudden naturally occurring stimulus from pain, fear, or anger. In uncontrolled trials, cyanotic episodes were reduced in frequency and severity by tetrabenazine (n=15) and additional inspired oxygen (n=10). Eight patients died suddenly and unexpectedly (four during cyanotic episodes). Twenty eight patients underwent physiological studies during cyanotic episodes. There was no evidence of seizure activity at the onset and although prolonged absence of inspiratory effort with continued expiratory efforts was common, breathing sometimes continued. Episodes were not caused by upper airway obstruction and sometimes occurred during positive airway pressure ventilation. The rapidity of fall in arterial oxygen pressure and continued breathing suggested a right to left shunt of sudden onset. The results of contrast echocardiography and lung imaging studies confirmed that this was occurring within the lungs.

These cyanotic episodes included both intrapulmonary shunting and prolonged expiratory apnoea. They are best explained by interactions between central sympathetic activity, brainstem control of respiration and vasomotor activity, reflexes arising from around and within the respiratory tract, and the matching of ventilation to perfusion in the lungs. They are a cause of sudden unexpected death in infancy and early childhood.

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In preliminary communications we have described our investigations of infants and young children presenting with cyanotic episodes.[1–4] These episodes were characterised by the rapid onset and progression of severe arterial hypoxaemia that was not caused by airway obstruction or seizures. Possible mechanisms included the rapid utilisation of reduced oxygen stores created by prolonged expiratory apnoea at low lung volumes, or the sudden development of areas of atelectasis resulting in a mismatch between ventilation and perfusion. Recent observations that severe hypoxaemia may develop rapidly despite continued spontaneous or mechanical ventilation have lead to further investigations. These, and the observations made from trials of treatment, have helped provide a better understanding of their pathophysiology.

Patients and methods

Fifty one infants and young children with recurrent episodes of cyanosis including loss of consciousness were studied. Thirty nine (76%) patients were otherwise healthy, and the remaining 12 had associated defects and congenital anomalies (table 1). The age range for the onset of the cyanotic episodes was 1 day to 22 months (median 7 weeks). Thirteen were 7 days old or less, 24 were 6 weeks old or less, and 39 were 4 months old or less at the time of their first episode. The range of birth weights was 1650–4280 g (median 3130 g). Four were born prematurely (case 18 at 36 weeks, 21 at 33 weeks, 25 at 34 weeks, and 29 at 31 weeks). A family history of cyanotic breath holding episodes in parents or siblings, or both was elicited in 24 (47%) and was unknown in three cases. Clinical assessment elicited no evidence of congenital heart lesions, upper airway obstruction, or lung parenchymal disorders.

In all 51 patients most of the cyanotic episodes began when the child was awake, usually after a naturally occurring stimulus such as pain, fear, or anger resulting in a cry or an attempt to cry. The stimulus was more often a sudden shock (with an 'element of surprise' or 'unexpectedness') rather than a gradually increasing provocation.[5] This presentation is

Table 1 Clinical details and case numbers

Clinical details	*No of children*	*Case No*
Otherwise healthy children	39	4–6, 9–14, 16–20, 23 26–37, 39–41, 43–51
Brainstem abnormalities:		
Meningomyelocele, Arnold-Chiari malformation	3	22, 24, 25
Developmental anomaly at pontomedullary junction	1	8
Medullary glioma	1	38
Brainstem disorder of unknown origin	1	2
Congenital alveolar hypoventilation	1	1
Primary sensory dysmyelination	1	42
Repaired tracheo-oesophageal fistula	3	3, 7, 21
Repaired vascular ring (and monosomy 9p)	1	15
Total	51	

identical to that described as 'cyanotic breath-holding'.[5] Episodes were more common when the patient was tired, when there was a high level of emotional tension in the home, or when the routine of the child was interrupted. The occurrence of a cyanotic episode seemed to create a vulnerable 10 minute period in which further episodes were more likely to occur. Infection, particularly respiratory, increased the frequency and severity of cyanotic events. In almost all cases parents spontaneously voiced their concern that their child might die during one of these events. Episodes commonly began with a series of expiratory cries without inspiratory efforts, often with a widely opened mouth. Sometimes an episode began with a single prolonged cry that was silent, the expiratory apnoea beginning immediately. If crying became established without prolonged apnoea or cyanosis, then an episode was unlikely to occur or be induced.

In six patients hypoxaemic episodes also began in other circumstances. In cases 8, 22, 24, and 25 (all of whom had brainstem anomalies) a smaller proportion of episodes (25%) occurred when quietly awake, when feeding, and when asleep. In cases 3, 7, and 21, who had undergone repair of tracheo-oesophageal fistulas, around 10%, 60%, and 90%, respectively, of their episodes were brought on by swallowing. Characteristically the patient would be eating solid food, some of which would seem to stick in the oesophagus. An attempt to cry would follow, then respiratory efforts would cease, and severe hypoxaemia would rapidly develop.

INVESTIGATIONS DURING CYANOTIC EPISODES

Because of their unpredictability only 28 patients underwent physiological recordings *during* cyanotic episodes. The remaining 23 had episodes with characteristic histories and clinical observations, and this suggested that the same underlying pathophysiology was operating. In the 28 cases investigated during episodes it was difficult to obtain optimal physiological data because of the need to institute resuscitative measures. Investigations were only performed with the fully informed consent of parents.

Radial artery samples were taken for measurement of oxygen pressure (PaO_2), carbon dioxide pressure ($PaCO_2$), and pH and the time from the onset of apnoea was noted in cases 2, 5, 8, 9, 18, 36, 50, and 51. Measurements were only documented when prolonged expiratory apnoea and cyanosis followed immediately after the initial attempt to cry.

Contrast echocardiograms were taken using an intravenous injection of micro air bubbles in 5% dextrose in cases 2, 5, 9, 10, 18, and 22.

Tape recordings (Racal Store 4) of the following signals were made in various combinations (n=28): (i) beat by beat oxygen saturation (median total response time 4 seconds) from a pulse oximeter (Nellcor N100 or N200) including the analogue signal representing each plethysmographic waveform used to derive the saturation in order to identify artefact (n=28)[5]; (ii) ribcage and abdominal movements from respiratory inductance plethysmography (Studley Data Systems) or from magnetometers or pressure capsules (n=28); (iii) electrocardiograms (n=28); (iv) airflow from a thermistor (Yellow Springs Instrument Co) or from expired carbon dioxide sampling (Engstrom Eliza) (n=28); (v) oesophageal pressure from a balloon catheter (PK Morgan) placed to detect both negative pressure changes with inspiration and cardiac artefact in cases 2–4, 10, and 18; (vi) electromyogram from the external oblique muscle in cases 2, 3, 4, 10, and 18); (vii) airflow integrated to volume using a facemask and pneumotachograph (Fleisch 00) in cases 2, 10, 18, and 22; (viii) arterial blood pressure from a radial artery line and Medex pressure transducer in cases 2 and 18; and (ix) pulmonary artery pressure (from an indwelling Swann Gantz catheter and Medex pressure transducer) in 22 hypoxaemic episodes in cases 10 and 18.

Chest fluoroscopy or chest radiographs were undertaken in cases 2, 8, 10, 18, and 22.

Electroencephalographic 8–12 channel recordings were made in cases 2–11, 13, 17, 18, 22–25, and 38.

Krypton-81m inhalation dynamic ventilation scans (cases 2 and 10) and krypton-81m infusion scans were done in patients 8, 10, 22, 30, and 46. Dextrose 5% was passed through a rubidium-81m column using an infusion pump, thus producing krypton-81m in solution. This solution was then infused continuously at a rate of between 6 and 10 ml/minute into a venous cannula in the hand. On reaching the lungs all the krypton crosses the alveolar to capillary membrane, thereby producing a scan of both lung fields. A shunt within the lungs results in ^{81m}Kr appearing in the systemic circulation and being detected outside the lung fields. During these scans a record of oxygen saturation was made at two second intervals.

Fibreoptic nasendoscopy was carried out under light general anaesthetic in cases 2, 3, 7, and 18.

The effects of breathing 15% oxygen (balance nitrogen) while awake and 18% oxygen (balance nitrogen) while asleep were investigated in case 10.

INVESTIGATIONS BETWEEN CYANOTIC EPISODES

Thirty two patients underwent overnight (roughly 12 hour) tape recordings of oxygen saturation, breathing movements, nasal airflow, and electrocardiography using the techniques described above.

Cases 3 and 32, at the ages of 7 and 9 years, respectively, underwent tape recordings of oxygen saturation, breathing movements, and nasal airflow before and during voluntary end expiratory breath holding for as long as they were able to, with nasal and oral airways occluded.

CONTROLS AND THEIR INVESTIGATIONS

Overnight tape recordings were compared with similar data collected from randomly selected healthy infants or children (40 in the neonatal period, 67 in the second month, 20 in the third,

Table 2 Radial artery blood gas measurements during cyanotic episodes

Case No	Before cyanotic episodes		During cyanotic episodes			Time from onset of apnoea (seconds)
	Arterial oxygen saturation* (%)	PaO_2 (kPa)	PaO_2 (kPa)	pH	$PaCO_2$ (kPa)	
2†	Not measured	14·0	2·1	7·39	5·1	20
5†	Not measured	12·7	3·0	7·37	5·1	14
8	94	Not measured	2·7	7·43	5·0	18
9	98	Not measured	4·2	7·30	5·1	10
18	98	Not measured	2·8	7·37	4·6	25
36	100	Not measured	3·9	7·39	5·2	15
50	98	Not measured	3·8	7·38	4·5	15
51	99	Not measured	2·9	7·37	5·1	20

*From pulse oximeter (Nellcor N200); †from Southall *et al.*[1]

18 in the sixth, seven in the 12th month, and 24 between 1 and 6 years of age).

Nine healthy, adult volunteers (age 21 to 46 years) underwent tape recordings of breathing movements, oral airflow, and oxygen saturation using the equipment described above, and were asked to breathe out maximally at the end of a normal tidal breath then to hold their breath for as long as possible. The durations of apnoea and the maximum falls in oxygen saturation were documented. In addition, two of the adults underwent krypton-81m infusion scans during which they performed end expiratory breath holding.

TRIALS OF TREATMENT

As cyanotic episodes were precipitated by behaviour associated with stimulation of the sympathetic nervous system and were accompanied by increases in pulmonary artery pressure (see below), tetrabenazine (a centrally acting α-adrenergic antagonist) in doses of 1·0 mg/kg/day in three to four divided doses was given to 15 patients with fully informed parental consent. This therapeutic trial was uncontrolled. Continuous additional inspired oxygen (delivered at 1–2 l/minute using a cannula placed on the upper lip with a fractional inspiratory oxygen (FiO_2) of 35–40%) was given to 10 patients. A combination of tetrabenazine and additional inspired oxygen was given to cases 8 and 22.

Results

FINDINGS DURING CYANOTIC EPISODES

From direct observations by parents, nursing, and medical staff the development of central cyanosis was rapid (within 5–10 seconds of the onset of the breath holding). After 25–30 seconds of progressively severe cyanosis there was a loss of consciousness with opisthotonus or a tonic convulsion, or both. Although surface electroencephalograms showed no seizure activity preceding the cyanosis, at between 25 and 30 seconds into the episode large amplitude slow waves (2 Hz) appeared within all leads with a subsequent lowering of voltage.

Values of arterial oxygen pressure (PaO_2) from radial artery cannulas at specified times after the onset of prolonged expiratory apnoea are shown in table 2. Accurate measurements of oxygen saturation on tape recordings during cyanotic episodes was often not possible because of movement artefacts. In those with adequate signals, arterial oxygen saturation values fell below 50% during all cyanotic episodes recorded.

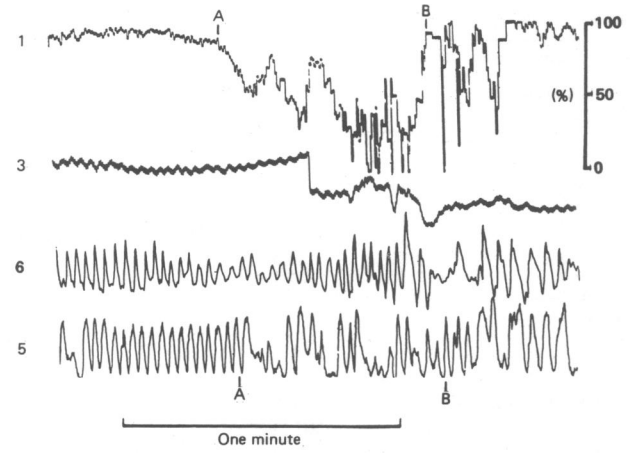
Details of the most common accompanying respiratory pattern, prolonged expiratory apnoea, have been previously reported.[1–3] In around 2% of the cyanotic episodes in which airflow from expired carbon dioxide measurements had been recorded, continued airflow signals were present throughout the hypoxaemic episode (fig 1A and E).

Chest radiographs showed high diaphragms but no atelectasis (results of cases 2 and 10 from reference 1). Krypton-81m inhalation scans showed rapid but incomplete emptying of gas from each lung (37% in 5 seconds and 40% in 11 seconds for case 2, 50% in 32 seconds for patient 10; values corrected for the decay of krypton-81m).[3] Intravenous krypton-81m scans during cyanotic episodes showed an increase in counts over the lung fields coinciding with an increase in mean background body counts (background increase in case 8 from 659 to 1085 (65%), in case 10 from 525 to 856 (63%), in case 22 from 487 to 685 (41%), in case 30 from 303 to 426 (41%), and in case 46 from 613 to 809 (32%)). Mean background body counts during voluntary expiratory apnoea for mean durations of 30 and 50 seconds in the two adult controls changed respectively from 129 to 135 (5%) and 70 to 76 (9%).

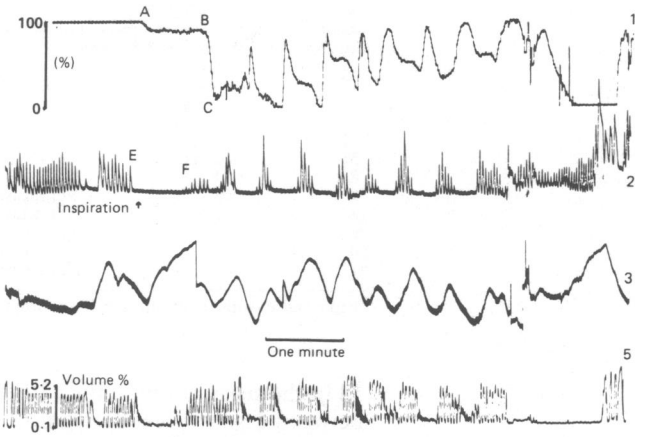
Contrast echocardiography showed no right to left intracardiac passage of air bubbles during cyanotic episodes (results of cases 2 and 5 from reference 1). In addition, no ductus arteriosus was detected in these patients.

The heart rate increased to above 170 bpm at the onset of an episode (fig 2A) but fell to below 80 bpm during the subsequent severe hypoxaemia (fig 2A and B). In around 5% of episodes asystole (≥2·0 seconds) or slow idioventricular escape rhythms occurred at this time. Systemic arterial blood pressure was transiently raised (by 10 to 25 mm Hg) at the onset of the episode in five of nine recorded instances (fig 2A and B). During bradycardia there was an increase in systemic arterial pulse pressure (fig 2A and B) in six of nine recorded instances.

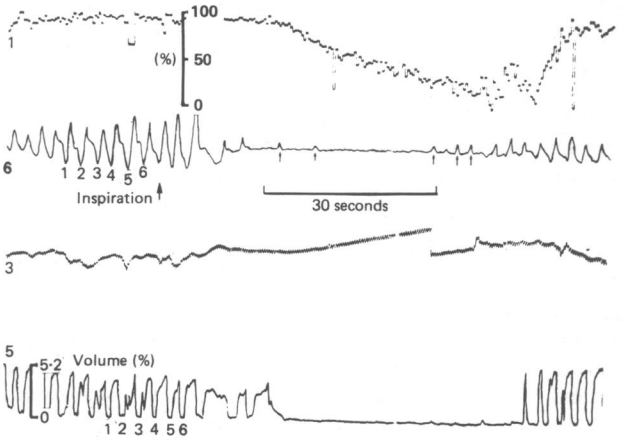
Pulmonary arterial blood pressure was increased during all episodes of hypoxaemia (figs 2A and B) beginning to rise in around a third of instances before the arterial oxygen saturation decreased (as measured using the pulse oximeter in the beat to beat mode (fig 2A). The increase in pulmonary artery pressure included both the diastolic and systolic components with little change in pulse pressure



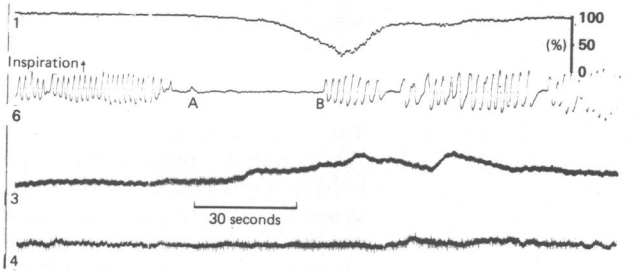
(A) A cyanotic episode that followed a cry and resolved spontaneously without resuscitation. Expiratory airflows and breathing movements continued throughout.



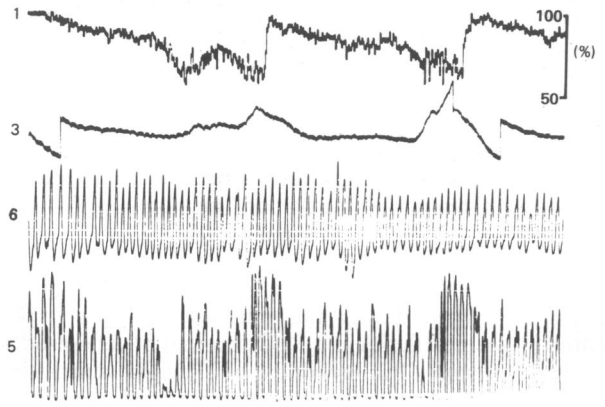
(B) During sleep there was a short apnoeic pause (**E–F**) accompanied by a small fall (**A–B**) in arterial oxygen saturation. The latter was followed by a major fall in arterial oxygen saturation (**B** to **C**) and subsequently there was an intermittent hypoxaemia accompanied by an episode of periodic apnoea that resolved spontaneously.



(C) Self resolving episode of severe hypoxaemia during sleep. Breathing efforts continued (↑) despite absent airflow. There was no bradycardia.



(D) Self resolving episode of severe hypoxaemia during sleep after a prolonged (37 seconds) apnoeic pause (**A** to **B**). There was only a slight fall in heart rate.



(E) Self resolving episodes of hypoxaemia during sleep despite continued breathing movements and continued expiratory airflow. There was no bradycardia.

Figure 1 *Comprises five recordings made on case 22 at age 3 months. Signals include (1) beat to beat arterial oxygen saturation from a pulse oximeter (total response time 4 seconds); (2) respiratory inductance plethysmography from a vest placed over the ribcage and abdomen; (3) plethysmographic waveform signals from which arterial oxygen saturation values were computed by the pulse oximeter; (4) electrocardiogram; (5) expired carbon dioxide from a cannula within the external nares (total response time 2·5 seconds); and (6) abdominal wall expansion from a pressure capsule transducer.*

until bradycardia developed. Pulmonary artery pressures before hypoxaemia ranged from 22/4 to 30/24 mm Hg. At their maximal values they ranged from 53/40 to 105/65 mm Hg.

Fibreoptic endoscopy during cyanotic episodes showed an initial vocal cord adduction (reported in cases 2, 3, and 7 in reference 1). In nine patients (cases 1–3, 5, 18, 22, 23, 33, and 38), cyanotic episodes continued despite bypass of the upper airway using an endotracheal tube or tracheostomy. Hypoxaemic episodes also occurred in five of these (1, 2, 18, 22, and 23) despite intermittent positive airway pressure ventilation (IPPV).

When attempting to resuscitate patients using bag and facemask ventilation, there was pronounced difficulty in inflating the lungs initially. Even when the upper airway was bypassed

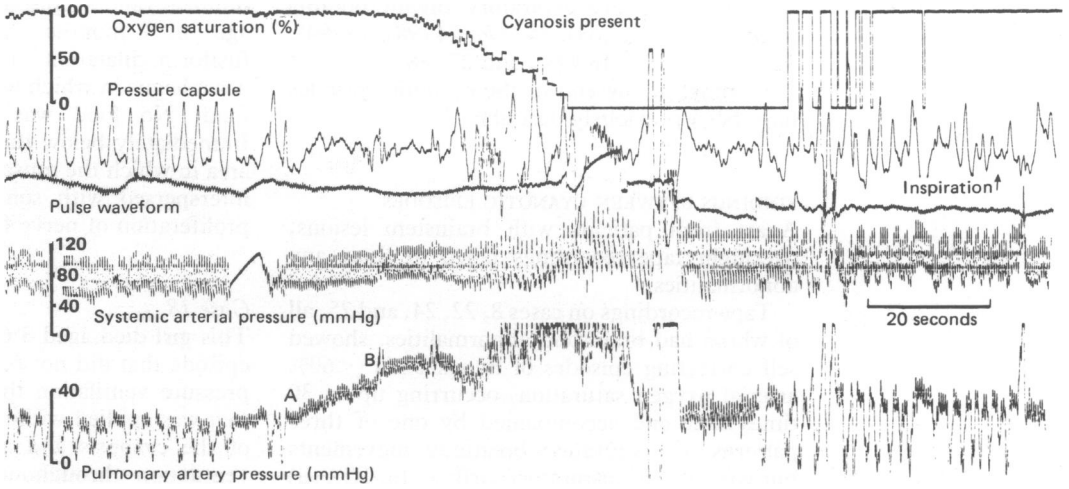


*Figure 2 (A) An episode of severe hypoxaemia in case 18 (who had a tracheostomy). Allowing for a 4 second total response time of the oximeter, pulmonary artery pressure increased (**A** to **B**) before arterial oxygen saturation began to fall. Pulmonary artery pressure continued to rise while hypoxaemia progressed reaching a peak value of 77/49 mm Hg. At this point there was a bradycardia and increase in pulse pressure in both systemic and pulmonary arteries. The loss of systemic arterial pressure at the onset of the episode was probably artefactual.*

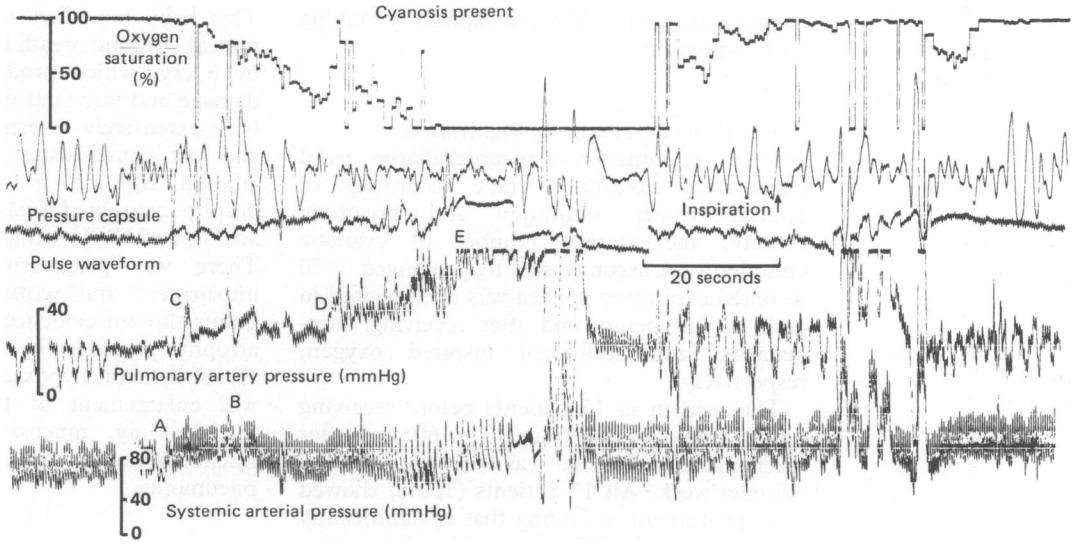


*Figure 2 (B) A further cyanotic episode in case 18. On this occasion the pulmonary artery pressure increased (**C** to **D**) from the beginning of the fall in arterial oxygen saturation. The rate of rise in pulmonary artery pressure increased as hypoxaemia became more severe (**D** to **E**). At the onset of the cyanotic episode there was an increase (**A** to **B**) in systemic blood pressure.*

using a tracheostomy or endotracheal tube, large inflation pressures were required. With recovery, effective inflation pressures rapidly decreased.

In case 21 (who had undergone repair of a tracheo-oesophageal fistula) cyanotic episodes were reproducibly induced by inflating a latex balloon (length 45 mm, diameter 10 mm) within the upper third of the oesophagus. Oesophagoscopy showed a fusiform dilatation above a strictured area at the site of the original repair. Episodes requiring resuscitation and subsequent ventilation continued, however, despite dilatation of this stricture. He subsequently underwent an aortopexy and Nissen fundoplication, after which episodes were reduced from every two or three days to every one or two weeks. Case 3, who had undergone repair of a tracheo-oesophageal fistula, underwent tracheostomy because acute airway obstruction caused by tracheomalacia was considered to be the cause of his hypoxaemic episodes. About nine out of 10 of his episodes occurred after crying rather than with swallowing. Even with a special tracheostomy tube inserted to lie 1 cm above the carina, there was no reduction in the frequency or severity of his episodes.

In case 10, 18% inspired oxygen given by a headbox during sleep produced cyanosis with oxygen saturation of less than 50%, prolonged expiratory apnoea, and arousal. (The effects of breathing 15% oxygen when awake in this subject have been reported by Southall *et al.*[1])

End expiratory breath holding manoeuvres in cases 3 and 32 produced the following maximum apnoeic pauses and falls in arterial oxygen saturation: 19 and 21 seconds with a saturation of 95 and 93% (case 32), 9 and 13 seconds with a saturation of 98 and 95% (case 3).

The duration of apnoea (seconds) and in brackets the lowest arterial oxygen saturation values (%) attained by nine adult controls

during forced end expiratory breath holding were: 31 (87), 15 (84), 25 (87), 24 (98), 19 (94), 32 (79), 27 (92), 18 (96), and 27 (88).

Findings at the end of the cyanotic episodes have been previously described.[1-3]

FINDINGS BETWEEN CYANOTIC EPISODES

Apart from patients with brainstem lesions, overnight tape recordings failed to show any abnormalities.

Tape recordings on cases 8, 22, 24, and 25, all of whom had brainstem abnormalities, showed self correcting episodes of hypoxaemia (<60% arterial oxygen saturation) occurring up to 30 times/hour and accompanied by one of three patterns: (i) continued breathing movements but with absent inspiratory airflow (fig 1C); (ii) prolonged absence (>20 seconds) of breathing efforts (fig 1D); and (iii) continued breathing movements and continued airflow (fig 1E). None of the overnight tape recordings of the control subjects showed prolonged apnoeic pauses (>20 seconds), hypoxaemia (arterial oxygen saturation <60%), or expiratory braking with hypoxaemia.

UNCONTROLLED TRIALS OF TREATMENT

From an examination of parental diaries, ward charts, and continuous tape recordings of arterial oxygen saturation and breathing activity, the average number of cyanotic episodes/week accompanied by prolonged (≥20 seconds) expiratory apnoea was documented in each patient before and after receiving tetrabenazine and additional inspired oxygen, respectively.

The median in 15 patients before receiving tetrabenazine was 14 (range 3 to 60) and after receiving tetrabenazine was 0 (range 0 to 25) episodes/week. All 15 patients (100%) showed an improvement, a finding that is significantly different from the 50% expected by chance (one sided binomial test, $p=0{\cdot}00003$).

The median before additional inspired oxygen in 10 patients was 21 (range 3 to 175) and after oxygen was 4 (range 0 to 35) episodes/week. Seven out of 10 showed an improvement, a finding that is significantly different from the 50% expected by chance (one sided binominal test, $p=0{\cdot}008$). Cases 8 and 22 were receiving additional inspired oxygen when tetrabenazine was added.

The recent addition of a small dose of clonidine to the tetrabenazine appeared more effective than tetrabenazine alone.

OUTCOME

Four patients died suddenly during or directly as a consequence of a cyanotic episode.

Case 7

This girl had undergone repair of a tracheo-oesophageal fistula and died aged 2·9 years while swallowing solid food. This seemed to stick in her oesophagus, she developed severe cyanosis, and died before reaching hospital. Similar cyanotic episodes had occurred since the age of 3 months.[7] At necropsy there was fusiform dilatation of the upper third of the oesophagus in which was lodged a piece of solid food. No food was found in the airway. Immediately below the dilatation there was an area in which the muscle of the oesophagus was interspersed with some fibrotic tissue and a proliferation of nerve fibres.

Case 18

This girl died aged 3·6 years during a cyanotic episode that did not respond to positive airway pressure ventilation through her tracheostomy that was applied within 20 seconds of the onset of the cyanosis and accompanied by definite ventilation throughout the entire attempt at resuscitation. At necropsy there was a small area of bronchopneumonia, and mucus in the trachea and bronchi.

Case 23

This baby boy died aged 11 months after a typical cyanotic breath holding episode induced by a cry, which produced irreversible brain damage and was fatal within 48 hours. He had been extensively investigated for such episodes and had a tracheostomy in place to aid resuscitation. Episodes had occurred before death despite continued inspiratory and expiratory airflow and IPPV through a tracheostomy tube. There was progressive neurodevelopmental impairment and sequential computed tomograms showed evidence of progressive cerebral atrophy, probably the result of his episodes of severe cerebral hypoxaemia. At necropsy there was enlargement of the trachea below the tracheostomy, mucosal inflammation of the tracheobronchial tree, and areas of bronchopneumonia.

Case 27

This girl died aged 1·5 years during a typical cyanotic breath holding episode after a cry. She had a cleft palate and had suffered a total of seven similar episodes, which had begun only four weeks before her death.[7] At necropsy there was pulmonary oedema but no structural abnormality of the airway.

Four additional boys (cases 35, 38, 41, and 48) each giving a history of typical cyanotic breath holding episodes died aged 2, 35, 5, and 6 months, respectively. These deaths were all sudden and unexpected; all four were found dead when their parents awoke in the morning. In all but case 38 there was no adequate explanation for the death at necropsy.

A necropsy on case 35 showed milk curds in the larynx, intrathoracic petechial haemorrhages, and pulmonary oedema. The cause of death was given as 'sudden infant death syndrome (milk aspiration)'.

Case 38 had had severe cyanotic episodes since he was 4 months of age. On the night before death, at the age of 2·9 years, he had had a severe episode of cyanosis accompanied as

usual by profuse sweating. The following morning he was found dead and at necropsy a glioma was found in the medulla.[8]

A necropsy on case 41 showed congested airways and haemorrhagic pulmonary oedema. The cause of death was given as acute bronchopneumonia (probably viral).

A necropsy on case 48 showed numerous petechial haemorrhages on the visceral pleura, epicardium, and intrathoracic thymus. Pulmonary oedema was also present. The cause of death was given as sudden infant death syndrome.

Cases 2, 8, 10, 17, 18, 23, and 34 had neurodevelopmental impairment that seemed to progress during times at which episodes were most frequent and severe.

Discussion

All our patients had cyanotic episodes associated with recurrent loss of consciousness. The most common trigger was a sudden, naturally occurring stimulus from pain, fear, or anger. These episodes are therefore equivalent to cyanotic breath holding with our patients at the severe end of the range of this common paediatric problem.[5] Although our patients presented early in life, the age at onset and the incidence of a positive family history is similar to that described by Lombroso and Lerman.[5] The 28 of our patients who underwent physiological recordings, however, had severe and frequent episodes that were considered to be life threatening. Investigations to gain a better understanding of their pathophysiology, and uncontrolled trials of treatment, were considered essential. Even in those patients with the most frequent and severe episodes, the relatively unpredictable timing, the need for resuscitation, and ethical concerns limited the information that could be collected.

Characteristically the onset of severe cyanosis was rapid (within 5–10 seconds), with loss of consciousness at around 25–30 seconds. Although prolonged expiratory apnoea and laryngeal adduction were features of the cyanotic episodes, severe hypoxaemia sometimes occurred despite continued airflow (figs 1A and 1E), endotracheal intubation, and IPPV. These features exclude primary upper airway obstruction as the cause of hypoxaemia.

Prolonged expiratory apnoea will contribute to hypoxaemia by reducing the content of oxygen available to perfused alveoli.[1] Accepting the rapid total circulatory times of infants and young children at rest (5–9 seconds),[9] is this mechanism alone sufficient to cause such severe hypoxaemia? Only a mild degree of hypoxaemia was documented after end expiratory breath holding in two of our patients, in our adult controls, and by Findley *et al.*[10] There is, however, limited value in comparing adults with infants because of differences in their closing volumes. Nevertheless the development of severe hypoxaemia, despite IPPV or continued spontaneous ventilation, suggests that apnoea contributed to, but was not the main cause of, the hypoxaemia. Moreover, during imposed airway obstruction,[11] hypoxaemia sufficient to produce electroencephalographic changes of cerebral hypoxia occurred after a delay of 60–70 seconds compared with only 25–30 seconds in our patients.

The rapid onset and progression of severe hypoxaemia in the presence of continued ventilation, together with the appearance of infused krypton outside the lung fields, suggested a right to left shunt. As contrast echocardiography failed to show an intracardiac pathway, the shunt must have been intrapulmonary.

Krypton infusion scans do not allow the shunt to be quantified. During apnoea, background counts may increase due to raised concentrations of krypton in pulmonary veins. Adult controls, however, did not show increased background counts during prolonged expiratory apnoea. Future studies with technetium labelled microspheres may provide more information on the size of the shunt.

Intrapulmonary shunting may arise from the continued or increased perfusion of unventilated alveoli (small airway obstruction or atelectasis) or from the diversion of a proportion of pulmonary arteriolar blood into pulmonary venules without contact with a gas exchanging surface. In previous reports we suggested that a shunt might have resulted from atelectasis caused by a primary defect in lung surfactant.[2] Our data continue to show reduced lung compliance during the latter part of each episode.[1–3] The results of radiographic and krypton imaging during the cyanosis, however, together with the increase in pulmonary artery pressure that sometimes preceded the fall in arterial oxygen saturation (fig 2A) suggests that although the shunt may have resulted from atelectasis or small airway closure it was more likely to have arisen from a primary disturbance in the distribution of pulmonary blood flow. An increase in pulmonary vascular resistance and therefore in pulmonary artery pressure after the hypoxaemia would be expected. A rise in pulmonary artery pressure before the hypoxaemia, however, suggests that an intrapulmonary shunt is a consequence as well as a cause of the increased pulmonary artery pressure. Whether the latter is the result of increased cardiac output or increased pulmonary vascular resistance cannot be answered from our data. Lung perfusion scans in newborn lambs,[12] and in adult humans who developed pulmonary oedema at high altitude,[13] have shown that the pulmonary vasoconstriction that results from airway hypoxia is not uniform; the accompanying increase in pulmonary artery pressure redistributes flow and produces a shunt that is accompanied by an increased filtration of fluid across the alveolar-capillary junction. As to the site of the shunt, bronchopulmonary and other anatomical arteriovenous anastomoses have been described in the human lung,[14] and recently Wilkinson and Fagan (Intrapulmonary arteriovenous shunting in cot deaths. Presented at the 35th meeting of the Paediatric Pathology Society, 1989) using a 2% gelatin solution and microspheres (64 μ in diameter) injected into the pulmonary artery showed that a proportion of infants who died suddenly had intrapulmonary arteriovenous pathways by-

passing the pulmonary capillary bed. Moreover, young infants have an increased tendency to venous admixture, which is thought to be related to a paucity of alveoli compared with lung capillaries.[15] Increased perfusion of this immature gas exchanging surface may also lead to a shunt.

Modifications to airway PO_2 have provided additional support for the role of pulmonary vasoconstriction in the genesis of the shunt. Thus an increased FiO_2 reduced the frequency and severity of episodes and, in one patient, a reduced FiO_2 precipitated cyanotic episodes. Moreover, cyanotic episodes were sometimes precipitated by short normal apnoeic pauses, (fig 1B) a natural mechanism for producing transient airway hypoxia. Changes in pulmonary vasomotor tone in response to airway PO_2 levels, may be mediated through the pulmonary neuroendocrine cell system, airway cells that may influence ventilation to perfusion matching.[16] In the fetus, which has a low lung liquid PO_2, these cells may help to maintain pulmonary vasoconstriction.[17] Disturbances in the number, size, or innervation of these cells, perhaps following chronic prenatal or postnatal airway hypoxia, may predispose to intrapulmonary shunting.[18]

The observation that stimuli known to induce sympathetic activity precipitate cyanotic episodes, together with the uncontrolled results of treatment with tetrabenazine, latterly in combination with clonidine, suggest that pulmonary vasoconstriction, mediated by adrenergic pathways, is a primary component in the genesis of the shunt. As prolonged expiratory apnoea and hypoxaemia continued to occur in response to crying despite an FiO_2 of 1·0,[1] adrenergic discharge may over-ride the protection provided by a high airway PO_2.

A mild degree of cyanosis on crying is common in most young children, suggesting that a degree of intrapulmonary shunting is possible in otherwise healthy subjects. In our patients with severe hypoxaemic episodes it is possible that there is a functional or structural potential for increased shunting in the pulmonary vascular bed, that there is an excessive adrenergic discharge, or that there is an enhanced response to a fall in airway PO_2, or all three.

Five patients had brainstem abnormalities and similar cyanotic episodes have been previously reported in patients with meningomyelocoeles,[19] and with brainstem tumours.[8] Brainstem defects may produce these cyanotic episodes by a number of different mechanisms including disturbances to the respiratory generators, to the centres controlling pulmonary vasomotor tone, and to the processing of reflexes arising in the pulmonary vascular bed or lung. Long has shown that stimulation of the brainstem vasomotor centre in piglets can induce pulmonary vasoconstriction.[20]

The cyanotic episodes that follow tracheo-oesophageal fistula repair,[21] or occur in patients with vascular rings,[22] may also result from mechanical stimulation of the trachea or oesophagus. In one patient, hypoxaemia followed balloon inflation within the oesophagus, supporting previous observations that absent inspiratory efforts and not obstructed inspiratory efforts were present during cyanotic episodes in patients with similar anomalies.[21 22] Fearon and Shortreed also induced absent inspiratory efforts under light general anaesthetic when a bronchoscope was passed through the compressed area of trachea, a response that was not seen with deep anaesthesia.[22] In addition, abnormal nerve fibres around the oesophagus were seen at necropsy in case 7, who died during a cyanotic episode induced by a bolus of food that lodged within the oesophagus.[7] Afferent impulses from around the trachea and oesophagus may therefore also precipitate intrapulmonary shunting, possibly through reflexes involving sympathetic efferent activity from the brainstem.[20]

The mechanisms responsible for the prolonged expiratory apnoea that accompanied and contributed to the hypoxaemia remains uncertain. A degree of breath holding normally follows emotional stimuli in many infants and young children,[23] but in our patients this response is prolonged for reasons which remain at present unknown. Evidence that prolonged apnoea may occur with noradrenergic stimulation of the brainstem may be relevant to this latter observation.[24] Pulmonary C fibre receptors[25] may also be stimulated by a pulmonary transudate in the alveolar-capillary junction resulting from pulmonary vasoconstriction.[12]

The first breaths that occur as the cyanotic episode ends show expiratory braking, a variable dynamic lung compliance, a continued increase in lung volumes following the end of each inspiratory effort, and variability of ventilation on the krypton inhalation scans.[1-3] Changes in compliance may result from induced defects in the lung surfactant system,[2] from pulmonary oedema, and from areas of decreased pulmonary capillary filling leading to loss of erectile support.[26]

As eight of our 51 patients (16%) died suddenly and unexpectedly (four during a cyanotic episode) the mechanisms outlined above are a potential pathway to sudden death in infancy and early childhood. The compatibility of this hypothesis with some of the known epidemiological, physiological, and pathological features of sudden unexplained infant death syndrome (SIDS) has been considered.[27] Additional evidence is given by the age of onset of these cyanotic episodes (similar to SIDS) and our observation that disturbances in daily routine, reported in association with SIDS,[28] were accompanied by an increased number of cyanotic episodes in our patients. The timescale of SIDS (sparing the first 4 weeks, peaking from 6 weeks to 4 months) may represent a vulnerable period related to postnatal remodelling and control of the pulmonary vascular bed.[29] The higher incidence of SIDS after a suboptimal prenatal environment might be related to the impact of fetal lung fluid hypoxia on the development of the pulmonary vasculature or neuroendocrine systems.[30-32] Kinney and Filiano, using neurochemical techniques, have shown that there are disturbances in the region of the brainstem vasomotor centres in SIDS victims.[33] The presence of pulmonary

oedema in almost all babies who die of SIDS may also be the result of intrapulmonary shunting.[34] The presence of petechial haemorrhages in babies who die of SIDS has also been produced experimentally by hypoxaemia and by noradrenaline infusion.[35]

In conclusion, the cyanotic episodes described here were accompanied by severe arterial and cerebral hypoxaemia. They have been previously described as cyanotic breath holding attacks, and are induced both by behavioural activity and in response to afferent impulses arising from within and around the respiratory tract. The resulting intrapulmonary shunt and prolonged expiratory apnoea are probably mediated through the brain stem vasomotor and respiratory control centres. As these episodes may cause sudden death and neurological impairment, we suggest that they should be subject to further research and to trials of treatment, particularly when they occur in young infants or are accompanied by recurrent loss of consciousness.

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